The Environment and Autism

U.S. EPA's Office of Research and Development

October 23, 2014

Purpose

- **Issue**
  - **Real public concern around prevalence of autism in the United States and desire to understand potential role of environmental factors**
  - **Recent high visibility research publications associating environmental factors and risk of autism**
  - **Results of latest studies suggest a compelling role for EPA**

- **Approach**
  - **What do we know: Review scientific evidence**
  - **What are we doing: Outline current EPA research activities in the context of research sponsored across the US government**
  - **What else could we do: Suggest additional actions**

Autism - Background

- **Definition:**
  - Autism spectrum disorder (ASD) is a group of developmental disabilities that can cause significant social, communication and behavioral challenges.
  - A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome
- **Prevalence:**
  - CDC estimates ASD affects roughly 1 in 68 children in the US (aged 8 years, period covered 2010)
    - Almost 5 times more common among boys (1 in 42) than among girls (1 in 189)
  - Globally, the prevalence of ASD is estimated to be 1 in 132 persons (Baxter et al, 2014)
- **Trends:**
  - Change in percentage of children ages 5 to 17 years old in US reported to have ever been diagnosed with autism has increased from 0.1 percent in 1977 to 1.0 percent in 2010. (America's Children and the Environment (ACE) report, 2013)
  - Globally, after accounting for methodological variations, there is no clear evidence of a change in prevalence for ASD between 1990 and 2010. (Global Burden of Disease Study, Baxter et al, 2014)
- **Costs to Society:**
  - Additional costs associated with caring for children with ASD estimated to be $17,000-21,000 per child annually (Lavelle, 2014)
  - Total cost for support during lifespan of an individual ranges from $1.4 -2.4 million (Buescher, 2014)
  - Estimated that total societal costs of caring for children with ASD were over $9 billion in 2011 (CDC)

Causes of Autism

- Emerging understanding suggests a complex, dynamic system of metabolic and immune anomalies involving many organ systems, including the brain, in association with environmental exposures
- Evidence points to pregnancy and the early postnatal period as critical windows of vulnerability
- **Genetic Risk Factors:** Understanding of role of genes has been significantly refined in recent years. Data suggest that approximately 40-60% of ASD risk can be attributed to inherited, common variation (SNPs).
- **Environmental Risk Factors (anything not genetic):**
  - Factors replicated in two or more studies include: protective effect of prenatal vitamin intake, and risks from prenatal maternal infection, preterm birth, advanced parental age at conception
  - Risks associated with modifiable exogenous exposures (e.g., environmental contaminants)
    - Limited studies in this area
    - Largest number of studies to date has addressed associations of increased ASD risk with air pollution exposure during gestation and/or early infancy
    - Suggestive evidence that exposure to endocrine disrupting chemicals such as pesticides, including organophosphates and phthalates may be associated with ASD
- **Gene-Environment Interactions:** GxE interactions are suspected to be of major importance in ASD. First studies demonstrating specific interactions just coming out. Role of epigenetic processes is a new area of investigation.

Evidence for Environmental Risk Factors: Modifiable Exogenous Exposures

- **To date, research in this area is limited and complexity of the exposures, ASD etiology, and health outcomes make it difficult to draw direct associations with exposures to environmental chemicals**
- Significant associations of increased ASD risk with air pollution exposure during gestation and/or early infancy (such as living near a freeway)
  - Living near freeway
  - Ozone, particulate matter, NOx
  - PAHs
- Suggestive evidence that exposure to pesticides may be associated with ASD
  - Residential proximity to pesticides
  - Organophosphates
- Gene-Environment interactions (air pollution)
  - Volk 2014 study finding that children with both a genetic risk factor and prenatal exposure to air pollutants experienced increased risk for ASD.
  - This is one of the first demonstrations of a specific interaction between a well-established genetic risk factor and an environmental factor that independently contribute to autism risk.

Von Ehrenstein 2014, air pollutants

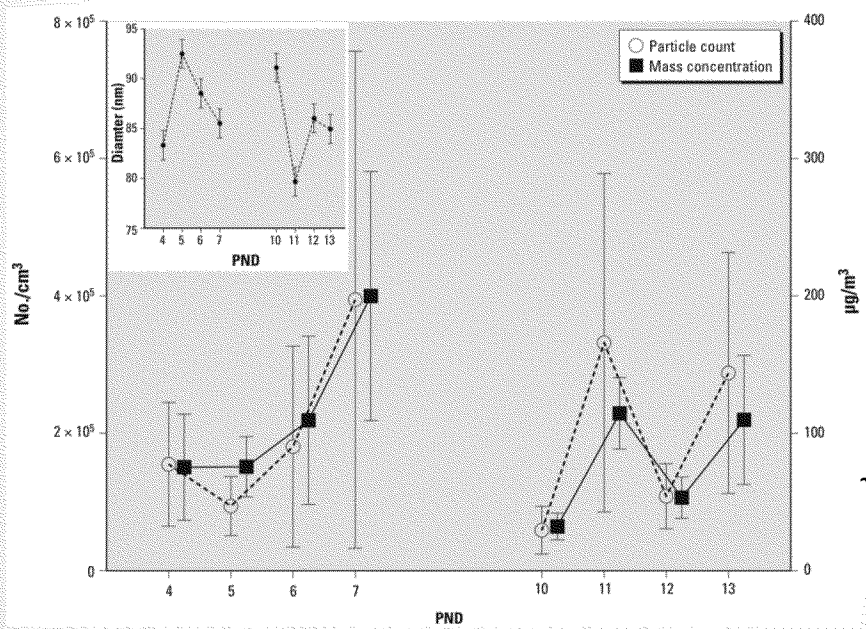
- Cohort of children born in LA County, CA from 1995-2006, residing within 5-km buffer around an air toxics monitoring station; Birth records linked to records of children diagnosed with primary autistic disorders
- Exposure assignment: monthly average air toxic exposures during pregnancy – monthly averages used to estimate trimester exposures
  - 4 monitors in LA County, collected 24-h integrated samples every 12 days
  - Conducted factor analysis to examine correlation structure between the air toxics and identify characteristics of potential sources that may emit these toxics
- Autism risks were increased for several correlated toxics mostly loading on 1 factor including:
  - 1,3-butadiene (OR = 1.59 [95% CI = 1.18–2.15])
  - meta/para-xylene (1.51 [1.26–1.82])
  - other aromatic solvents, lead (1.49 [1.23–1.81])
  - perchloroethylene (1.40 [1.09–1.80])
  - formaldehyde (1.34 [1.17–1.52])
- **Population-based evidence of increased risks for autism in children, subsequent to in utero exposure to traffic- and industry-related ambient air toxics, including aromatic solvents, butadiene, lead, and chlorinated solvents**
- Von Ehrenstein et al. (2014): In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism. Epidemiology Jul 22 (Epub ahead of print)

Shelton 2014, proximity to pesticides

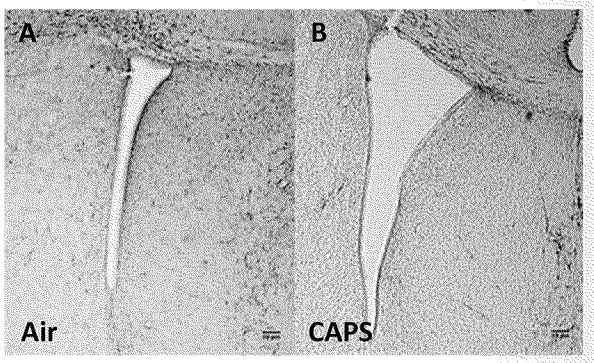
- The CHARGE study is a population-based case-control study of ASD, developmental delay (DD), and typical development.
  - Commercial pesticide application data from the California Pesticide Use Report (1997-2008) were linked to mother's addresses during pregnancy
  - Estimated the odds ratio (OR) of exposure comparing confirmed cases of ASD (n = 486) or DD (n = 168) with typically developing referents (n = 316).
- **Results showed increased risk of ASD and DD for children of mothers that lived, during pregnancy, within 1.5km of an agricultural pesticide application.**
  - Proximity to organophosphates at some point during gestation was associated with a 60% increased risk for ASD
    - 3rd trimester exposures: **OR = 2.0, [95% CI = (1.1, 3.6)]**
    - 2nd trimester chlorpyrifos applications: **OR = 3.3 [95% CI = (1.5, 7.4)]**
  - Pyrethroid: Children of mothers residing nearby just prior to conception or during 3rd trimester were at greater risk for both ASD and DD; **OR's ranging from 1.7 to 2.3**
  - Carbamate: Risk for DD was increased but no specific vulnerable period was identified.
- Shelton et al. Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. Environmental Health Perspectives, 2014; DOI: 10.1289/ehp.1307044 (EPA supported)

Allen 2014, Effects of CAPs in Mice

- Investigated the mechanism(s) by which exposure to ultrafine concentrated ambient particles (CAPs) adversely influences central nervous system development
  - Observed brain region– and sex-dependent alterations in cytokines and neurotransmitters in both male and female CAPs-exposed mice
  - Lateral ventricle dilation (i.e., ventriculomegaly) was observed only in CAPs-exposed male mice
- **Ventriculomegaly is a neuropathology that has been associated with poor neurodevelopmental outcome, autism, and schizophrenia; study adds to the evidence suggesting a causal association between exposure to air pollution and neurodevelopmental abnormalities**



Mean particle counts and particle mass concentration for each day of exposure. Inset: mean diameter for each day of exposure.



Images of lateral ventricles from control (A) and exposed (B) mice at postnatal day 14 show enlargement resulting from exposure to CAPs.

- matter air pollution: persistent ventriculomegaly, neurochemical 122(9):939–945 (2014).

Volk et al, 2014, GxE

- In previous independent studies, authors have identified
  - Increased ASD risk among children exposed to high levels of local near-roadway traffic related air pollution and regional particulate matter near the time of birth
  - Increased ASD risk among children with the C allele of the *MET* gene promoter variant rs1858830,4,5 which is associated with decreased expression of MET protein in brain and immune system
- **In this study, subjects with both *MET* rs1858830 CC genotype and high air pollutant exposures were at increased risk of autism spectrum disorder compared with subjects who had both the CG/GG genotypes and lower pollutant exposures.**
  - No increased risk of ASD for the *MET* CC genotype compared with CG/GG genotypes (crude OR=0.9 [95%CI= 0.6–1.4]).
  - ASD associated with exposure to the top quartile of traffic-related air pollution (1.7 [1.0–2.7]), particulate matter less than 10 microns in diameter (2.5 [1.6–4.3]), particulate matter less than 2.5 microns in diameter (1.9 [1.2–3.1]), and nitrogen dioxide (1.7 [1.1–2.7]).
  - Synergistic effects observed between *MET* CC genotype and local traffic-related air pollution (2.9 [1.0–10.6]), regional PM_{10} (3.2 [1.3–9.1]), and **regional nitrogen dioxide exposure (3.6 [1.3–13])**
  - A statistical test of multiplicative interaction identified a **statistically significant effect between NO2 and *MET* CC genotype (p=0.03)** and borderline significant effects between local traffic-related air pollution and *MET* CC genotype (p=0.09).
- **This is one of the first demonstrations of a specific interaction between a well-established genetic risk factor and an environmental factor that independently contribute to autism risk**
- Volk et al, 2014. Autism Spectrum Disorder: Interaction of Air Pollution with the MET Receptor Tyrosine Kinase Gene. Epidemiology 25(1):44-47. (EPA supported)

Current EPA Research Activities

- **EPA/NIEHS Children's Center at University of California, Davis** focused on the role of toxicant exposure, immunologic, and genetic risk factors contributing to the incidence and severity of childhood autism
  - 3 awards 2001, 2006 and 2011 from EPA and NIEHS
  - total EPA funding of $11.2M (matched by NIEHS)

- Significant intramural and extramural research focused on assessing the potential for environmental chemicals to alter processes essential for development of the nervous system (not designed specific to autism)
  - Recent research in ORD has used tests to look at impulsivity and attention in animal models following developmental exposure to xenobiotics. These endpoints may be related to several portions of the autistic spectrum described in humans.
  - Past ORD research has employed developmental exposure to several compounds (PCBs, mercury, lead) that have been associated with changes in cognitive function and symptomology associated with autism disorders.
  - Additionally, considerable research in ORD has focused on development as a susceptible life stage for exposure to environmental chemicals. This work is designed to determine the sensitivity of developing organisms to chemicals and the mechanisms underlying sensitivity.

Research Activities Across Federal Government

- **Interagency Autism Coordinating Committee (IACC)**
  - Established in accordance with the Combating Autism Act of 2006, reauthorized 2011 (Public Law 112-32)
  - Federal Members of IACC include Director NIH, Director NIEHS, Director NICHD, FDA, DOD, HHS, DOEd (currently EPA does not have a role)
  - Strategic Plan, 2009, updated April 2014, objectives associated with elucidating causes of ASD emphasize
    - Understanding how environmental risks may differ in vulnerable subgroups
    - Applying emerging science in epigenetics, the microbiome, animal models of ASD and bioinformatics
- **GAO report May 20, 2014 on coordination of federal autism activities**
  - The GAO found that apart from federal agencies' participation on the IACC, there were limited instances of agency coordination
  - 1,206 autism research projects funded by 12 federal agencies
  - Five Agencies fund a total of 159 research activities focused on elucidating causes of autism. Primarily NIH followed by DOD and CDC. EPA included under category “other agencies” with one activity
- **BRAIN Initiative announced by President Obama April 2013 on World Autism Day**
  - June 5, 2014 NIH released a scientific vision for 4.5 billion dollar investment over 10 years beginning in 2016
  - Early results include application of 3-D map collating activity of genes in 300 brain regions during mid-prenatal development to demonstrate relationship between genetic risk factors for ASD and early brain development.

Potential for Additional EPA Actions

- Identify strategic niche where EPA leadership is required to advance understanding of ASD risks
- Provide formal EPA representation to IACC and relevant subcommittees
- Convene meeting of EPA Administrator and NIH Director to discuss opportunities for coordination
- Identify priorities for EPA research in line with EPA Strategic Plan